REMARKS

Reconsideration of the present application is respectfully requested in view of the Amendment submitted herewith and the following remarks. Claims 1, 3, 4, and 6-18 were pending. Amendments to the specification have been made solely to correct typographical errors referring to Table numbers in the Examples. To point out more clearly and to claim distinctly certain embodiments of Applicants' invention, claims 1, 7, 8, and 18 have been canceled, claims 3, 4, 6, and 9-17 have been amended, and claims 19-23 have been added. Accordingly, upon entry of this Amendment, claims 3, 4, 6, 9-17, and 19-23 are currently under examination. The Amendment submitted herewith is not to be construed as acquiescence to the stated grounds for rejection and is made without prejudice to prosecution of any subject matter modified or removed by this Amendment in a related divisional, continuation, or continuation-in-part application. No new subject matter has been added. Support for the amended and new claims may be found throughout the specification, for example, at page 7, lines 4-15; page 13, lines 3-7; page 14, line 23 through page 15, line 2; page 21, lines 4-30; page 22, lines 1-5; page 24, lines 4-5; page 37, lines 11-17; and page 39, line 23 through page 40, line 6.

REJECTIONS UNDER 35 U.S.C. § 103

Part I. In the Office Action dated August 24, 2005, the Examiner rejects claims 1, 3, 4, 6, and 10-18 under 35 U.S.C. § 103(a) for allegedly being obvious over U.S. Patent No. 5,726,292 ('292) (Lowell) in view of Anselem et al. (PCT International Publication No. WO 94/26255). The Examiner concedes that '292 fails to teach the use of bioadhesive nanoemulsions. However, the Examiner alleges that Anselem teaches that nanoemulsions may be used in combination with other adjuvant systems, including proteosomes, and that nanoemulsions may be formulated with bioadhesive additives to enhance delivery of antigens to mucosal surfaces. The Examiner alleges that combining the teachings of '292 with the teachings of Anselem regarding bioadhesive nanoemulsions would be obvious to a person having ordinary skill in the art.

Part II. In this Action, page 5, paragraph 11, the Examiner indicates that the rejection of claims 7, 8 and 18 for being obvious "over Lowell as applied to claims 1, 3, 4, 6, and 10-17 above," and further in view of VanCott (*J. Immunol. Meth.* 183:103-117 (1995)) has been withdrawn. However, the heading of paragraph 11 indicates that the prior rejection was restated and maintained although no restatement was provided. Applicants kindly request clarification regarding whether the basis for this rejection has been obviated and request clarification with respect to which Lowell document the Examiner refers. Nevertheless, Applicants respectfully submit that the present claims are nonobvious over any cited Lowell reference in view of VanCott. Applicants refer the Examiner to remarks presented regarding the rejection set forth in paragraph 12 (page 5) of this Action (see Part III herein).

Part III. The Examiner rejects claims 1, 3, 4, 6, 7, 8, 10, 11, and 16-18 under 35 U.S.C. § 103(a) for allegedly being obvious over "the 292 patent, Lowell, or Lowell in view of VanCott as applied above, and further in view of WO 95/11700." Applicants assume that the Lowell document to which the Examiner refers is Lowell et al. (*Science* 240:800-02 (1988)); although as noted above, the reference to "Lowell" in these rejections is unclear given that Lowell is the first author or first named inventor on at least three of the cited documents.

Part IV. The Examiner maintains and restates the rejection of claim 9 under 35 U.S.C. § 103(a) for allegedly being obvious "over the 292 patent or Lowell, in view of WO 95/11700, and further in view of VanCott and Desai" (*Proc. Natl. Acad. Sci. USA* 83:8380-84 (1986)).

Part V. The Examiner rejects claims 1, 6-13, and 16-18 under 35 U.S.C. § 103(a) for allegedly being obvious over Anselem or WO 95/11700 in view of the teachings of VanCott or Desai. The Examiner asserts that each of Anselem and WO 95/11700 teach use of nanoemulsions in combination with proteosomes as adjuvants for the induction of an immune response against HIV gp160 antigens. The Examiner concedes that neither Anselem nor WO 95/11700 teach the use of oligomeric forms of gp160 proteins nor teach that the protein comprises the sequence set forth in residues 33-681 of SEQ ID NO:1. The Examiner further asserts that VanCott teaches that oligomeric HIV gp160 is effective for inducing neutralizing

anti-HIV antibodies and that Desai teaches an HIV gp160 sequence that comprises a region having an amino acid sequence identical to residues 33-681 of SEQ ID NO:1. The Examiner alleges that a person having ordinary skill in the art would have a reasonable expectation of success to achieve Applicants' invention by combining the teachings of the cited documents.

Applicants respectfully traverse these rejections and submit that the present claims as amended herewith meet the statutory requirements for nonobviousness under 35 U.S.C. § 103. Applicants submit that the PTO has not established a *prima facie* case of obviousness under any of the stated grounds for rejection. *See In re Mayne*, 104 F.3d 1339, 1341-43, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997) (The PTO has the burden of showing a *prima facie* case of obviousness.). The PTO must show (1) that the references teach or suggest all claim limitations; (2) that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that the combined teachings of the references indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. When rejection of claims depends upon a combination of prior art references, something in the prior art as a whole must suggest the desirability, thus the obviousness, of making the combination (*see In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998)).

The present claims are directed, in pertinent part, to an immunogenic composition comprising (a) an antigen that comprises a C-terminal truncated gp160 protein, wherein the C-terminal truncated gp160 protein includes the endogenous hydrophobic amino acid sequence set forth at positions 523-551 of SEQ ID NO:1; and (b) proteosomes, wherein the proteosomes are complexed or coupled with the antigen, and (c) bioadhesive nanoemulsions, wherein the composition elicits neutralizing antibodies to HIV in a subject upon administration of the composition to the subject, and wherein the neutralizing antibodies are present in one or more of vaginal secretions, intestinal secretions, lung secretions, and feces. In a certain embodiment, the antigen further comprises an exogenous hydrophobic material comprising about 3 to about 50 non-polar or uncharged amino acid residues. In other certain embodiments, the C-terminal truncated gp160 protein is a C-terminal truncated gp160 oligomer. In a specific embodiment, the

amino acid sequence of the C-terminal truncated gp160 protein consists essentially of the amino acid sequence set forth at residues 33-681 of SEQ ID NO:1.

Part I. (Rejection of claims 1, 3, 4, 6, and 10-18 for allegedly being obvious over U.S. Patent No. 5,726,292 ('292) (Lowell) in view of Anselem et al. (PCT International Publication No. WO 94/26255.))

Applicants respectfully submit that '292 (U.S. Patent No. 5,726,292) and Anselem et al. (PCT International Publication No. WO 94/26255), each taken alone or in combination, fail to teach or suggest the subject matter of the present claims. The documents, alone or in combination, do not teach or suggest each and every feature of the currently claimed embodiments of Applicants' invention. As noted in the Action, the Examiner agrees that '292 does not teach or suggest an immunogenic composition that comprises the combination of an antigen, proteosomes, and bioadhesive nanoemulsions. Furthermore, each of '292 and Anselem does not teach or suggest an immunogenic composition that comprises a C-terminal truncated gp160 protein that includes the endogenous hydrophobic amino acid sequence set forth at positions 523-551 of SEQ ID NO:1. Accordingly, neither cited document alone or in combination teaches or suggests each feature of the present claims.

Neither '292 nor Anselem provides any teaching, suggestion, or motivation to combine or modify the teachings of either document to achieve Applicants' claimed embodiments. Moreover, given the understanding of gp160 in the art, a person having ordinary skill in the art would not reasonably expect to achieve an immunogenic composition comprising a C-terminal truncated gp160 protein complexed or coupled with proteosomes. As understood in the art, the HIV envelope gene encodes the glycoprotein gp160 that is further processed to yield two structural protein portions, gp120 and gp41. The latter portion, gp41, is located at the C-terminal end of gp160 and is the transmembrane portion (*see, e.g.,* specification, page 4, lines 11-18 and references cited therein; Desai et al., *Proc. Natl. Acad. Sci. USA* 83:8380-84 (1986), at page 8383). The transmembrane gp41 moiety of gp160 comprises a membrane-spanning hydrophobic domain, and it also contains amphipathic regions believed to bind to the plasma membrane (*see, e.g.,* specification, page 6, lines 13-25; Yang et al., *Proc. Natl. Acad. Sci. USA*

92:9871-9875 (1995) (Reference No. 36 as listed on Form 1449 submitted January 24, 2002)). Therefore, a person having ordinary skill in the art would reasonably expect that a carboxy terminal truncation of gp160 in the transmembrane gp41 portion would remove one or more hydrophobic portions of transmembrane gp41 (*e.g.*, about 3 to about 50 endogenous non-polar or uncharged amino acid residues) and concomitantly expect that such a C-terminal truncated gp160 protein would be unable to form a complex with proteosomes. In the absence of the disclosure of the subject application, an ordinarily skilled person, therefore, would not reasonably expect to obtain an immunogenic composition that comprises a C-terminal truncated gp160 protein complexed or coupled with proteosomes, and thus would not reasonably expect to obtain an immunogenic composition as recited that had the capability to elicit neutralizing antibodies against HIV in an immunized subject.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established and that the claimed subject matter is nonobvious as required under 35 U.S.C. § 103. Applicants therefore respectfully request that the rejection of the claims be withdrawn.

Parts II and III. (Rejection of claims 7, 8, and 18 for allegedly being obvious "over Lowell as applied to claims 1, 3, 4, 6, and 10-17 above," and further in view of VanCott (*J. Immunol. Meth.* 183:103-17 (1995)) and/or rejection claims 1, 3, 4, 6, 7, 8, 10, 11, and 16-18 for allegedly being obvious over "the 292 patent, Lowell, or Lowell in view of VanCott, and further in view of WO 95/11700.)

Applicants respectfully submit that '292 (U.S. Patent No. 5,726,292), Lowell et al. (*Science* 240:800-02 (1988)), referred to herein as "Lowell (*Science*)," or Lowell et al. in view of VanCott et al. (*J. Immunol. Meth.* 183:103-17 (1995)), referred to herein as VanCott, and further in view of PCT International Publication No. WO 95/11700 (Lowell et al.), referred to herein as WO 95/11700, each taken alone or in combination fail to teach or suggest the currently claimed embodiments of Applicants' invention. Each of '292, Lowell (*Science*), VanCott, and WO 95/11700 does not teach or suggest an immunogenic composition comprising a C-terminal truncated gp160 protein that includes the endogenous hydrophobic amino acid sequence set forth at positions 523-551 of SEQ ID NO:1. VanCott describes only a gp160 polypeptide that forms

oligomers and that is isolated from a cell line infected with the 451 HIV isolate, but fails to teach or suggest a clone that produces a C-terminal truncated gp160 polypeptide as described in the subject application and recited in the instant claims.

As noted in the Action, the Examiner agrees that '292 does not teach or suggest an immunogenic composition that comprises an antigen and proteosomes in combination with bioadhesive nanoemulsions. Applicants submit that Lowell (*Science*) and VanCott also both fail to teach or suggest an immunogenic composition that comprises an antigen and proteosomes in combination with bioadhesive nanoemulsions. This deficiency is not remedied by WO 95/11700 because none of the four cited documents teach or suggest an antigen comprising a C-terminal truncated gp160 protein. Accordingly, none of the cited documents, alone or in combination, teaches or suggests each feature of the present claims.

Furthermore, none of the cited documents provides any teaching, suggestion, or motivation to combine or modify the teachings of any other document or documents to achieve Applicants' claimed embodiment. Moreover, as discussed above in Part I, a person having ordinary skill in the art would not reasonably expect that a C-terminal truncated gp160 protein would form a complex with proteosomes. Thus, also as discussed above in Part I, given the understanding of gp160 in the art, a person having ordinary skill in the art would not reasonably expect to achieve an immunogenic composition that comprises the recited features and that is capable of inducing neutralizing antibodies against HIV that are present in one or more of vaginal secretions, intestinal secretions, lung secretions, and feces in an immunized subject. The HIV envelope gene encodes the glycoprotein gp160 that is further processed to yield two structural protein portions, gp120 and gp41. The latter portion, gp41, is located at the C-terminal end of gp160 and is the transmembrane portion (*see, e.g.,* specification, page 4, lines 11-18 and references cited therein; Desai et al., *Proc. Natl. Acad. Sci. USA* 83:8380-84 (1986), at page 8383). The transmembrane gp41 moiety of gp160 comprises a membrane-spanning hydrophobic domain, and it also contains amphipathic regions believed to bind to the plasma membrane (*see, e.g.,* specification, page 6, lines 13-25; Yang et al., *Proc. Natl. Acad. Sci. USA* 92:9871-9875 (1995) (Reference No. 36 of Form 1449 submitted January 24, 2002)). Therefore, an ordinarily skilled person would reasonably expect that a carboxy terminal truncation of gp160 in the

transmembrane gp41 portion would remove one or more hydrophobic portions (*e.g.*, about 3 to about 50 endogenous non-polar or uncharged amino acid residues) of transmembrane gp41 and concomitantly expect that such a C-terminal truncated gp160 protein would be unable to be complexed or coupled with proteosomes.

Accordingly, in the absence of the disclosure of the subject application, an ordinarily skilled person would not reasonably expect to obtain successfully an immunogenic composition comprising an antigen that comprises a C-terminal truncated gp160 protein, complexed or coupled with proteosomes and combined with bioadhesive nanoemulsions, and thus would not reasonably expect to obtain the presently claimed immunogenic composition that has the capability to elicit neutralizing antibodies against HIV in an immunized subject. Applicants therefore respectfully submit that a *prima facie* case of obviousness has not been established and that the claimed subject matter is nonobvious as required under 35 U.S.C. § 103. Applicants respectfully request that this rejection of the claims be withdrawn.

Part IV. (The Examiner rejects claim 9 for allegedly being obvious over '292 (U.S. Patent No. 5,726,292) or Lowell (*Science*), in view of WO 95/11700, and further in view of VanCott and Desai et al. (*Proc. Natl. Acad. Sci. USA* 83:8380-84 (1986)), referred to herein as "Desai.")

Claim 9 is presently directed in pertinent part to the immunogenic compositions as recited, wherein the amino acid sequence of the C-terminal truncated gp160 protein consists essentially of the sequence set forth at residues 33-681 of SEQ ID NO:1. Each of '292, Lowell, VanCott, WO 95/11700, and Desai fail to teach or suggest an immunogenic composition that comprises a C-terminal truncated gp160 protein comprising the endogenous hydrophobic amino acid sequence set forth at positions 523-551 of SEQ ID NO:1. In addition, each of the cited documents fails to teach or suggest a C-terminal truncated gp160 protein that consists essentially of the amino acid sequence as set forth at residues 33-681 of SEQ ID NO:1.

Desai describes a polynucleotide sequence and the encoded polypeptide sequence for a CDC451 HIV isolate; however, Desai fails to teach or suggest an immunogenic

composition that comprises a C-terminal truncated gp160 protein, and further fails to teach or suggest that the amino acid sequence of a C-terminal truncated gp160 protein may consist essentially of the amino acid sequence set forth at residues 33-681 of SEQ ID NO:1. VanCott describes an oligomeric gp160 polypeptide that is isolated from a cell line infected with the 451 HIV isolate, but fails to teach or suggest a clone of the cell line that produces a C-terminal truncated gp160 polypeptide as described in the subject application and recited in the present claims.

Desai and VanCott also fail to teach or suggest an immunogenic composition that comprises proteosomes and fail to teach or suggest an immunogenic composition that comprises an antigen complexed or coupled with proteosomes in combination with bioadhesive nanoemulsions. As noted in this Action and as discussed above, the Examiner agrees that '292 does not teach or suggest an immunogenic composition that comprises an antigen and proteosomes in combination with bioadhesive nanoemulsions. Applicants submit that each of '292, Lowell (*Science*), VanCott, and Desai fails to teach or suggest an immunogenic composition that comprises an antigen complexed or coupled with proteosomes in combination with bioadhesive nanoemulsions. This lack of teaching is not remedied by WO 95/11700 because none of the five cited documents teach or suggest an antigen comprising a C-terminal truncated gp160 protein, and none teach or suggest that in certain embodiments, a C-terminal truncated gp160 protein consists essentially of the amino acid sequence as set forth at residues 33-681 of SEQ ID NO:1. Accordingly, none of the cited documents alone or in combination teaches or suggests each feature of the present claims.

Furthermore, none of the cited documents provides any teaching, suggestion, or motivation to combine or modify the teachings of any other document or documents to achieve Applicants' claimed immunogenic compositions. Moreover, a person having ordinary skill in the art would not reasonably expect that an immunogenic composition comprising a C-terminal truncated gp160 protein that consists essentially of the amino acid sequence set forth at positions 33-681 of SEQ ID NO:1 and that thus lacks the terminal 187 amino acids residues of the transmembrane gp41 moiety of gp160 (*see, e.g.,* specification, page 21, lines 27-30) would form a complex with proteosomes. As discussed herein, the HIV envelope gene encodes the

glycoprotein gp160 that is further processed to yield two structural protein portions, gp120 and gp41. The latter portion, gp41, is located at the C-terminal end of gp160 and is the transmembrane portion (*see, e.g.,* specification, page 4, lines 11-18 and references cited therein; Desai et al., *Proc. Natl. Acad. Sci. USA* 83:8380-84 (1986), at page 8383). The transmembrane gp41 moiety of gp160 comprises a membrane-spanning hydrophobic domain, and it also contains amphipathic regions believed to bind to the plasma membrane (*see, e.g.,* specification, page 6, lines 13-25; Yang et al., *Proc. Natl. Acad. Sci. USA* 92:9871-9875 (1995) (Reference No. 36 of Form 1449 submitted January 24, 2002)). Thus, an ordinarily skilled person would reasonably expect that a carboxy terminal truncation of gp160 in the transmembrane gp41 portion that removes 187 amino acids (more than half of the gp41 polypeptide) would be incapable of forming a complex with proteosomes. An ordinarily skilled person would, thus, not reasonably expect to obtain successfully the claimed immunogenic composition that is capable of inducing neutralizing antibodies against HIV, which antibodies are present in one or more of vaginal secretions, intestinal secretions, lung secretions, and feces in an immunized subject.

Applicants therefore respectfully submit that a *prima facie* case of obviousness has not been established and that the claimed subject matter is nonobvious as required under 35 U.S.C. § 103. Applicants respectfully request that this rejection of the claims be withdrawn.

Part V. (Rejection of claims 1, 6-13, and 16-18 for allegedly being obvious over Anselem or WO 95/11700 in view of VanCott or Desai.)

Applicants respectfully submit that either Anselem or WO 95/11700 in view of VanCott and Desai fails to teach or suggest the currently claimed embodiments of Applicants' invention. Applicants submit that each of the cited documents, either alone or in any combination, fails to teach or suggest each feature of the amended claims as submitted herewith. Each of Anselem, WO 95/11700, VanCott, and Desai does not teach or suggest an immunogenic composition comprising a C-terminal truncated gp160 protein that includes the endogenous hydrophobic amino acid sequence set forth at positions 523-551 of SEQ ID NO:1. In addition, each of the cited documents fails to teach or suggest a C-terminal truncated gp160 protein that consists essentially of the amino acid sequence set forth at residues 33-681 of SEQ ID NO:1.

Desai describes a polynucleotide sequence and the encoded polypeptide sequence for the 451 HIV isolate genome; however, Desai fails to teach or suggest a C-terminal truncated gp160 protein as disclosed in the subject application. VanCott describes a gp160 polypeptide that forms oligomers and that is isolated from a cell line infected with a 451 HIV isolate, but fails to teach or suggest a clone of the cell line that produces a C-terminal truncated gp160 polypeptide that includes the endogenous hydrophobic amino acid sequence set forth at positions 523-551 of SEQ ID NO:1 as described in the subject application and recited in the present claims. VanCott and Desai also fail to teach or suggest an immunogenic composition that comprises proteosomes and further fail to teach or suggest an immunogenic composition that comprises any antigen and proteosomes in combination with bioadhesive nanoemulsions. Accordingly, the cited documents, alone or in combination, fail to teach or suggest each feature of the present claims.

Furthermore, none of the cited documents provides any teaching, suggestion, or motivation to combine or modify the teachings of any other document or documents to achieve Applicants' claimed embodiment. Moreover, as discussed herein, a person having ordinary skill in the art would not reasonably expect that an immunogenic composition comprising a C-terminal truncated gp160 protein would be complexed or coupled with proteosomes. Thus, the ordinarily skilled artisan would not reasonably expect to obtain the claimed immunogenic composition that has the capability to induce neutralizing antibodies against HIV in an immunized subject.

As discussed herein, the HIV envelope gene encodes the glycoprotein gp160 that is further processed to yield two structural protein portions, gp120 and gp41. The latter portion, gp41, is located at the C-terminal end of gp160 and is the transmembrane portion (*see, e.g.,* specification, page 4, lines 11-18 and references cited therein; Desai et al., *Proc. Natl. Acad. Sci. USA* 83:8380-84 (1986), at page 8383). The transmembrane gp41 moiety of gp160 comprises a membrane-spanning hydrophobic domain, and it also contains amphipathic regions believed to bind to the plasma membrane (*see, e.g.,* specification, page 6, lines 13-25; Yang et al., *Proc. Natl. Acad. Sci. USA* 92:9871-9875 (1995) (Reference No. 36 of Form 1449 submitted January 24, 2002)). Therefore, an ordinarily skilled artisan would reasonably expect that a carboxy terminal truncation of gp160 in the transmembrane gp41 portion (for example, a truncation

removing 187 amino acids at the carboxy terminal end) would remove one or more hydrophobic portions (*e.g.*, about 3 to about 50 endogenous non-polar or uncharged amino acid residues) of transmembrane gp41 and concomitantly expect that such a C-terminal truncated gp160 protein would be unable to be complexed or coupled with proteosomes.

An ordinarily skilled person would, therefore, have no reasonable expectation of successfully obtaining an immunogenic composition capable of inducing neutralizing antibodies to HIV in one or more of vaginal secretions, intestinal secretions, lung secretions, and feces in an immunized subject when such a C-terminal truncated gp160 protein is complexed or coupled with proteosomes in combination with bioadhesive nanoemulsions. Particularly, an ordinarily skilled person would not reasonably expect to obtain an immunogenic composition comprising a C-terminal truncated gp160 protein that consists essentially of the amino acid sequence set forth at residues 33-681 of SEQ ID NO:1 that is capable of inducing neutralizing antibodies to HIV in one or more of vaginal secretions, intestinal secretions, lung secretions, and feces in an immunized subject when such a C-terminal truncated gp160 protein is combined with proteosomes and bioadhesive nanoemulsions.

Accordingly, in the absence of the disclosure in the subject application, an ordinarily skilled person would not reasonably expect to obtain an immunogenic composition comprising the recited features that had the capability to induce neutralizing antibodies against HIV in an immunized subject. Applicants therefore respectfully submit that a *prima facie* case of obviousness has not been established and that the claimed subject matter is nonobvious as required under 35 U.S.C. § 103. Applicants respectfully request that this rejection of the claims be withdrawn.

REJECTIONS UNDER JUDICIALLY CREATED DOCTRINE OF DOUBLE PATENTING

Part I. The Examiner rejects claims 1, 3, 4, and 6-18 under the judicially created doctrine of double patenting as obvious over claims 1, 2, 5, 7, and 8 of U.S. Patent No. 5,726,292 ('292), further in view of either Anselem et al. (PCT International Publication

No. WO 94/26255)), referred to herein as Anselem, or International Patent Application Publication No. WO 95/11700 (WO 95/11700).

Applicants respectfully traverse this rejection and submit that a person skilled in the art would not find the subject matter of the present claims obvious over claims 1, 2, 5, 7, and 8 of '292, alone or in combination with either or both of Anselem and WO 95/117000. None of claims 1, 2, 5, 7, and 8 of '292 recite, nor does the detailed description of '292 teach or suggest, an immunogenic composition comprising (a) an antigen that comprises a C-terminal truncated gp160 protein, wherein the C-terminal truncated gp160 protein includes the endogenous hydrophobic amino acid sequence set forth at positions 523-551 of SEQ ID NO:1; and (b) proteosomes, wherein the proteosomes are complexed or coupled with the antigen, and (c) bioadhesive nanoemulsions, wherein the composition elicits neutralizing antibodies to HIV in a subject upon administration of the composition to the subject, and wherein the neutralizing antibodies are present in one or more of vaginal secretions, intestinal secretions, lung secretions, and feces. Moreover, neither Anselem nor WO 95/11700 alone or in combination with '292 teach or suggest an immunogenic composition that comprises an antigen comprising a C-terminal truncated gp160 protein as recited.

The '292 patent, alone or in combination with either or both of Anselem or WO 95/117000 provides no teaching, suggestion, or motivation to combine or modify the teachings of any document to achieve Applicants' claimed embodiments. Moreover, as discussed in detail above with respect to the rejections under 35 U.S.C. § 103, given the understanding of gp160 in the art, a person having ordinary skill in the art would not reasonably expect to achieve an immunogenic composition comprising a C-terminal truncated gp160 protein complexed or coupled with proteosomes. As understood in the art, the HIV envelope gene encodes the glycoprotein gp160 that is further processed to yield two structural protein portions, gp120 and gp41. The latter portion, gp41, is located at the C-terminal end of gp160 and is the transmembrane portion (*see, e.g.,* specification, page 4, lines 11-18 and references cited therein; Desai et al., *Proc. Natl. Acad. Sci. USA* 83:8380-84 (1986), at page 8383). The transmembrane gp41 moiety of gp160 comprises a membrane-spanning hydrophobic domain, and it also contains amphipathic regions believed to bind to the plasma membrane (*see, e.g.,* specification,

page 6, lines 13-25; Yang et al., *Proc. Natl. Acad. Sci. USA* 92:9871-9875 (1995) (Reference No. 36 of Form 1449 submitted January 24, 2002)). Therefore, a person having ordinary skill in the art would reasonably expect that a carboxy terminal truncation of gp160 in the transmembrane gp41 portion (for example, a truncation removing 187 amino acids at the carboxy terminal end) would remove one or more hydrophobic portions (*e.g.*, about 3 to about 50 endogenous non-polar or uncharged amino acid residues) of transmembrane gp41 and concomitantly expect that such a C-terminal truncated gp160 protein would be unable to be complexed or coupled with proteosomes. In the absence of the disclosure of the subject application, an ordinarily skilled person, therefore, would not reasonably expect that a C-terminal truncated gp160 protein would form a complex with proteosomes and thus would not reasonably expect to obtain the presently claimed immunogenic composition further comprising bioadhesive nanoemulsions that had the capability to induce neutralizing antibodies against HIV in an immunized subject.

Applicants respectfully submit that the presently claimed embodiments of Applicants' invention are nonobvious and that granting the present claims would not result in an unjustified extension of the term of '292. Accordingly, Applicants respectfully request that the rejection of these claims be withdrawn.

Part II. The Examiner also rejects claims 1, 3, 4, and 6-18 under the judicially created doctrine of double patenting as obvious over claims 1, 2, 5, 7, and 8 of U.S. Patent No. 5,726,292 ('292), further in view of either Anselem or WO 95/11700 and further in view of VanCott and Desai as described in the Action with respect to the rejections under 35 U.S.C. § 103(a).

Applicants respectfully traverse this rejection and submit that a person skilled in the art would not find the subject matter of the present claims obvious over claims 1, 2, 5, 7, and 8 of '292, alone or in combination with either Anselem or WO 95/11700 further in view of either VanCott or Desai. None of claims 1, 2, 5, 7, and 8 of '292 recite, nor does the detailed description of '292 teach or suggest, an immunogenic composition that comprises (a) an antigen that comprises a C-terminal truncated gp160 protein wherein the C-terminal truncated gp160 protein includes the endogenous hydrophobic amino acid sequence set forth at positions 523-551

of SEQ ID NO:1; (b) proteosomes, wherein the proteosomes are complexed or coupled with the antigen, and (c) bioadhesive nanoemulsions, wherein the composition elicits neutralizing antibodies to HIV in a subject upon administration of the composition to the subject, and wherein the neutralizing antibodies are present in one or more of vaginal secretions, intestinal secretions, lung secretions, and feces.

Applicants submit that each of the cited documents, either alone or in any combination, fails to teach or suggest each feature of the amended claims as submitted herewith. Each of '292, Anselem, WO 95/11700, VanCott, and Desai does not teach or suggest an immunogenic composition that comprises a C-terminal truncated gp160 protein comprising the endogenous hydrophobic amino acid sequence set forth at positions 523-551 of SEQ ID NO:1. In addition, each of the cited documents fails to teach or suggest a C-terminal truncated gp160 protein that consists essentially of the amino acid sequence set forth at residues 33-681 of SEQ ID NO:1. Desai describes a polynucleotide sequence and the encoded polypeptide sequence for the CDC451 HIV isolate genome; however, Desai fails to teach or suggest an immunogenic composition that comprises a C-terminal truncated gp160 protein and fails to teach or suggest that the amino acid sequence of a C-terminal truncated gp160 protein may consist essentially of the amino acid sequence set forth at residues 33-681 of SEQ ID NO:1 as disclosed in the subject application. VanCott describes a gp160 polypeptide that forms oligomers and that is isolated from a cell line infected with a 451 HIV isolate, but fails to teach or suggest a clone of the cell line that produces a C-terminal truncated gp160 polypeptide comprising the endogenous hydrophobic amino acid sequence set forth at positions 523-551 of SEQ ID NO:1 as described in the subject application and recited in the present claims. Desai and VanCott also fail to teach or suggest an immunogenic composition that comprises proteosomes complexed or coupled with an antigen comprising a C-terminal truncated gp160 protein in combination with bioadhesive nanoemulsions. Accordingly, '292 alone or in combination with any one or more of the cited documents fails to teach or suggest each feature of the present claims.

Furthermore, '292 in combination with any one or more of the cited documents provides no teaching, suggestion, or motivation to combine or modify the teachings of any other document or documents to achieve Applicants' claimed embodiments. Moreover, as discussed

with respect to the rejections under 35 U.S.C. § 103, an ordinarily skilled person would not reasonably expect that an immunogenic composition comprising a C-terminal truncated gp160 protein would form a complex with proteosomes. Thus, the ordinarily skilled artisan would not reasonably expect that such a composition would be an immunogenic composition having the capability to induce neutralizing antibodies against HIV in an immunized subject.

Also as discussed herein, the HIV envelope gene encodes the glycoprotein gp160 that is further processed to yield two structural protein portions, gp120 and gp41. The latter portion, gp41, is located at the C-terminal end of gp160 and is the transmembrane portion (*see, e.g.,* specification, page 4, lines 11-18 and references cited therein; Desai et al., *Proc. Natl. Acad. Sci. USA* 83:8380-84 (1986), at page 8383). The transmembrane gp41 moiety of gp160 comprises a membrane-spanning hydrophobic domain, and it also contains amphipathic regions believed to bind to the plasma membrane (*see, e.g.,* specification, page 6, lines 13-25; Yang et al., *Proc. Natl. Acad. Sci. USA* 92:9871-9875 (1995) (Reference No. 36 of Form 1449 submitted January 24, 2002)). Therefore, an ordinarily skilled artisan would reasonably expect that a carboxy terminal truncation of gp160 in the transmembrane gp41 portion (for example, a truncation removing 187 amino acids at the carboxy terminal end) would remove one or more hydrophobic portions (*e.g.,* about 3 to about 50 endogenous non-polar or uncharged amino acid residues) of transmembrane gp41 and concomitantly expect that such a C-terminal truncated gp160 protein would be unable to be complexed or coupled with proteosomes.

In the absence of the disclosure of the subject application, an ordinarily skilled person, therefore, would not reasonably expect that a C-terminal truncated gp160 protein would form a complex with proteosomes and thus would not reasonably expect to obtain the presently claimed immunogenic composition further comprising bioadhesive nanoemulsions that had the capability to induce neutralizing antibodies against HIV in an immunized subject. Applicants therefore respectfully submit that the presently claimed embodiments of Applicants' invention are nonobvious and that granting the present claims would not unjustifiably extend the term of '292. Accordingly, Applicants request that the rejection of these claims be withdrawn.

Applicants respectfully submit that pending claims 3, 4, 6, 9-17, and 19-23 are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

Mae Joanne Rosok
Registration No. 48,903

MJR:teb

Enclosure:
Postcard

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

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